A Terminal Disclaimer prepared in accordance with 37 C.F.R. §1.321(b) and (c) is enclosed. The signed Terminal Disclaimer will obviate the above obviousness-type double patenting rejection.

II. Rejection under 35 U.S.C. §102

Claims 1-8, 10-16, and 18-24 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by O'Neill *et al.* (WO 98/14610). This rejection is respectfully traversed.

A. The Invention

The present invention, as embodied by claim 1, provides for a method for performing multiplexed determinations of target nucleic acids. In the method, modified primer reagents are captured and selectively released.. Each primer reagent comprises a first sequence for hybridizing to a target and a second sequence for capture. The method further includes a capture reagent comprising a homologous sequence to the second sequence of the primer reagent; and a displacement reagent comprising a nucleic acid sequence that is homologous to each of the capture sequences. A modifying reagent system is employed for modifying primer reagents bound to the target nucleic acid. The method comprises combining the target nucleic acid with a plurality of the primer reagent comprising differing second sequences for differing first sequences, under hybridizing conditions in the presence of the modifying reagent system in an assay mixture, whereby primer reagent bound to target nucleic acid is modified. The modified primer reagent is combined with the capture reagent at a single site, whereby modified primer reagent is separated from other components in the assay mixture. The captured, modified primer reagent is sequentially released with the displacement reagent; and the modified primer reagent is determined.

B. The Prior Art

O'NEILL ET AL. describe multiplex polynucleotide capture methods and compositions in which the capture of the various primers occurs at distinct locations,

and wherein the release conditions for the various primers are substantially the same. The method of O'Neill *et al.* comprises mixing a plurality of recoverable primers with a plurality of polynucleotide sequencing templates. A plurality of polynucleotide sequencing ladders are generated, wherein each of the extension products is derived from one of the recoverable primers. The polynucleotide sequencing ladders are bound to recovery tag binding compounds, wherein the recovery tag binding compounds are immobilized in an addressable manner on one or more solid supports, and the polynucleotide sequencing ladders are separated from one another.

C. Analysis

The standard for lack of novelty, that is, for anticipation, is one of strict identity. To anticipate a claim for a patent, a single prior source must contain all its essential elements. M.P.E.P. § 2131

O'Neill *et al.* fail to show releasing sequentially the subsets of nucleic acid reagents from the sequestering agent by sequentially increasing stepwise the stringency conditions to provide separated subsets as in the present invention. For example, on page 19, lines 2-4, O'Neill et al. states, "Different recovery tags may be released by the same or different releasing procedures in given embodiments of the invention. Preferably, all recovery tags in a given embodiment of the invention are released by the same procedure." Thus, O'Neill et al. specifically requires that the same releasing procedure be used to release the different recovery tags. Similarly, on page 19, line 31 through page 20, line 3, O'Neill teaches that sets of recovery tags are preferably released under similar releasing conditions (denaturation conditions) to simplify the method.

In summary, O'Neill et al. fail to teach sequentially increasing stepwise the stringency conditions to effect release of the subsets of nucleic acid reagents.

Accordingly, applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102.

III. Rejection under 35 U.S.C. §103

Claims 1-16 and 18-24 were rejected under 35 U.S.C. §103 as allegedly obvious over O'Neill in view of Matthews *et al.* (*Anal. Biochem.*, 1988, 169:1-25).

Claims 1-24 were rejected as allegedly obvious over O'Neill *et al.* in view of Matthews *et al.* and further in view of Köster *et al.* (U.S. Patent No. 5,928,906).

These rejections are respectfully traversed.

A. The Present Invention

The present invention is described above.

B. The Cited Art

O'NEILL ET AL. is described above.

MATTHEWS ET AL. reviews various labels and strategies for DNA probe assays. Among the topics is solution hybridization of target DNA. In this method, the target DNA is hybridized to a quantitatable probe and separate ligand (i.e. biotin) in solution. The ligand then binds to the receptor on a solid support. In this manner, the quantitatable probe is bound to the solid support when hybridized to target DNA.

KÖSTER ET AL. describe processes and kits for simultaneously amplifying and sequencing single stranded target nucleic acid molecules, and performing high throughput DNA sequencing. The process involves contacting the target DNA with at least one primer that hybridizes to the target DNA, a set of chain elongating nucleotides, at least one chain terminating nucleotide, and a first and second DNA polymerase. The second DNA polymerase has a higher affinity for the chain terminating nucleotide than the first DNA polymerase such that polymerization by the first polymerase results in amplification and polymerization by the second polymerase results in the formation of chain terminated fragments. The chain terminated fragments are detected by detecting means such as polyacrylamide gel electrophoresis, capillary zone electrophoresis and mass spectrometry in conjunction with a visualization means. Finally, the fragments are aligned to determine the sequence of the single stranded nucleic acid. Köster *et al.*

further teaches that multiplexing can be achieved either by the composition or length of the sequence or by the introduction of mass-modifying functionalities into the primer oligonucleotide.

C. Legal Standard

In determining whether an invention is nonobvious, the burden is on the PTO to establish a case of *prima facie* obviousness, which requires that, (1) the prior art references teach or suggest all the limitations of the claim; (2) there is some suggestion or motivation in the prior art references or knowledge available to one of ordinary skill in the art to modify the references or to combine the teachings; and (3) there is a reasonable expectation of success (M.P.E.P. §2142).

D. Analysis: Rejection of claims based on O'Neill *et al.* in view of Matthews *et al.*

The shortcomings of O'Neill *et al.* are detailed above. The teachings in Matthews *et al.* do not make up for the deficiencies in O'Neill *et al.* Matthews *et al.* provides a review of various labels and strategies for DNA probe assays and does not discuss sequentially increasing stepwise the stringency conditions to effect release of subsets of nucleic acid reagents.

E. Analysis: Rejection of claims based on O'Neill *et al.* in view of Matthews *et al.* further in view of Köster *et al.*

The shortcomings of O'Neill *et al.* and Matthews *et al.* are detailed above. The teachings in Köster *et al.* do not make up for the deficiencies in O'Neill *et al.* and Matthews *et al.* Köster *et al.* is concerned with simultaneously amplifying and sequencing single stranded target nucleic acid molecules, and performing high throughput DNA sequencing. Nowhere does Köster *et al.* teach or suggest sequentially increasing stepwise the stringency conditions to effect release of subsets of nucleic acid reagents.

Accordingly, Applicant respectfully requests withdrawal of the rejections under 35 U.S.C. §103.

IV. Finality of Office action

Applicants request reconsideration of the finality of the rejection of the present Office action and that the finality of the action be withdrawn. This Office action is the first action on the merits in the instant application. According to MPEP §706.07(b), final rejections are proper on First Action in those situations where (A) the new application is a continuing application of, or a substitute for, an earlier application, and (B) all claims of the new application (1) are drawn to the same invention claimed in the earlier application, and (2) would have been properly finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Further, it would not be proper to make final a first Office action in a continuation-in-part application where any claim includes subject matter not present in the earlier application. A first action final should be made by using Form Paragraphs 7.41 or 7.41.03.

The instant application is a continuation-in-part of U.S. Application No. 09/354,629. The subject matter of at least claim 4 of the present application was not claimed in the priority application. Thus, at least the requirement that all claims of the new application be drawn to the same invention is not met.

Further, the Examiner has omitted Form Paragraph 7.41 or 7.41.03 from the Office action.

Accordingly, Applicants respectfully withdrawal of the finality of the Office action as premature.

V. Conclusion

In view of the foregoing, Applicant submits that the claims pending in the application comply with the requirements of 35 U.S.C. §112 and patentably define over the cited art. A Notice of Allowance is therefore respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4410.

Respectfully submitted,

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Date: March 25, 2002

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